Abiotrophy in Domestic Animals: A Review

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ABSTRACT

This review of abiotrophies in domestic animals has been organized by the predominate anatomical location of the lesion. Secondary considerations include the major signs of the clinical disorder and special neuropathological features. Those abiotrophies that have an established genetic basis are identified but the review includes degenerative disorders in which the etiology is not yet established.

Gowers in 1902 (1) gave a lecture entitled a "Lecture on Abiotrophy" in which he developed and applied the concept of abiotrophy as a pathological process. He applied this to the understanding of degenerative diseases of the nervous system. These diseases are characterized by the spontaneous degeneration of neurons prematurely. Once normal neurons are differentiated they continue to grow but do not divide and once having completed their development are expected to last the lifetime of the individual. The premature degeneration of these cells reflects an intrinsic abnormality in their structure which alters their metabolic activity resulting in their unexpected degeneration. Abiotrophy refers to this process. In contrast with the broader connotation of the term atrophy, abiotrophy limits the cellular defect to an inborn metabolic error of development and excludes exogenous insults that can cause the demise of the cell. The underlying cellular defect in most abiotrophies is inherited.

Abiotrophy is a pathological process by which we can classify a degeneration in the nervous system and it allows us to concentrate our efforts on determining the specific cytological defect that is present and ideally the genetic basis for its occurrence. When we use abiotrophy to name a disease, we are only describing the pathological process — a concept of the mechanism resulting in the degeneration that is described. As the underlying cause of the abiotrophy is determined, this should be used in naming the disease. Using the concept of abiotrophy in its broadest sense it is applicable to any of the inherited degenerative diseases of the nervous system. This would include the numerous cerebellar cortical degenerations about which we have little knowledge of the primary cellular defect in most instances. Abiotrophy also applies to the numerous examples of storage disease which affect neurons diffusely. In many of these the specific enzymatic defect is known as well as the mechanism of inheritance. These storage diseases are appropriately identified by the specific enzyme deficiency. Nevertheless the pathological process that results from this enzyme deficiency is an abiotrophy. Where our knowledge includes a unique feature of the abiotrophic process, the disease has been named by that pathological feature such as neuraxonal dystrophy, neurofilamentous disease and chromatolytic diseases. It must be remembered that these are just features reflecting the degeneration of the neuron which have a large variety of causes. Many of these are exogenous toxicities. Abiotrophy refers simply to those processes that are intrinsic to the neuron and limit its normal viability.

In considering a premature degeneration as a disease process, comparison can be made to normal neuronal development in which many populations of differentiated neurons die prematurely as a normal programmed developmental event. Some of the mechanisms may be common to both processes. This normal developmental event occurs in the peripheral nervous system when motoneurons from the ventral grey column fail to develop a normal motor end plate relationship with a skeletal muscle fiber which is the target organ. These neurons degenerate. The ultimate size and shape of the ventral grey column reflects this normal degenerative process (2,3). In the central nervous system the normal development of the mature visual system is a result of significant degeneration of retinal ganglion cells that failed to complete normal synapses on dendrites and soma of neurons in the lateral geniculate nucleus (4). The viability of the latter thalamic neurons is dependent on their normal synaptic development with neurons in the visual system's cerebral cortex in the occipital lobe.

Our goal as veterinary scientists is first to recognize and describe the abiotrophy and then to study it further to understand the intrinsic abnormality on a structural, biochemical and genetic basis. This will allow us to offer appropriate genetic counseling to prevent further occurrence of the disease and ultimately to offer therapy for patients by restoring the defective mechanism. The use of gene transfer mechanisms is now in its infancy but hopefully in the near future will permit the treatment of what are presently lethal diseases (5). The use of domestic animals that have diseases similar to those in people will be vital in these studies to achieve this therapeutic success.

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In this review of domestic animal abiotrophies, I have excluded the numerous storage diseases and leukodystrophies caused by specific lysosomal enzyme deficiencies. Biological processes often defy rigid systematic categorization. Regardless of the choice of classification, overlaps and exceptions will occur. I have chosen primarily an anatomic approach based on where the major lesion is located but this is influenced secondarily by the major presenting clinical signs or nature of the pathological process (Table I). The major groups include: 1) Motoneuron degenerative diseases. 2) Multisystem degenerations. These are further divided by the part of the neuron involved — cell body, process, myelin only — or by the major pathological feature that is present — neuraxonal dystrophy, neurofilamentous accumulations. 3) Cerebellar degenerations. 4) Miscellaneous degenerations. All of the diseases that are included here are degenerative processes. All are considered to be abiotrophies at the present level of our understanding. The genetic basis for some has been established. In others, only the lesions have been described but the cause remains unknown. Further investigation of some of these may confirm an extrinsic cause such as toxicity or nutritional deficiency rather than a genetic basis, and therefore exclude them from this classification of abiotrophies.

Although this is a review of nervous system abiotrophies the close clinical and morphological relationship of skeletal muscle to the nervous system warrants the observation that important muscle abiotrophies exist. Although muscle cells have the capability of regeneration, specific defects in their structural integrity can lead to their premature degeneration. In domestic animals these structural abnormalities can be morphologically very subtle but clinically very profound as in the congenital myotonic myopathy recognized in goats (6) and the Chow Chow dog (7). These are inherited disorders that are similar to Thomsen's disease in people. The other extreme in morphological deterioration of muscle is the sex-linked recessive myopathy of male Golden Retrievers (8) and Irish Terriers (9). The disease in Golden Retrievers has been found to be a nearly perfect animal model of

TABLE I.

Motoneuron Degenerations
- Swedish Lapland dog - Sandefeldt 1973 (19)
- Saint Bernard - Great Dane - Bloodhound Crosses - Stockard 1936 (20)
- Brittany Spaniel - Lorenz 1979 (20, 21)
- Rottweiler - Shell 1987 (26)
- English Pointer - Inada 1978 (28)
- German Shepherd - Cummings 1989 (31)

Multisystem Degenerations

Cell Body
- Cocker Spaniel - Zaggy 1988 (32)
- Cairn Terrier - Palmer, Cummings 1988 (33-35)
- Angora Goat - Lancaster 1987 (36)

Processes
- Simmental - Harper, Hartley 1989 (37, 38)
- Limousin X - Palmer, 1988/Harper 1989 (39, 40)
- Brown Swiss - Leipold 1973 (41)
- Smooth Fox Terrier - Bjorck 1957 (46)
- Jack Russell Terrier - Hartley 1973 (47)
- Bull Mastiff - Carmichael 1983 (49)
- German Shepherd - Averill 1973 (50)
- Horses (Appaloosa) - Mayhew 1977 (56)

Myelin
- Rottweiler - Gamble 1984 (60)
- Labrador Retriever - O'Brien 1985 (62)
- Dalmation - Bjerkas 1977 (64)
- Afghan Hound - Cummings 1978 (65)
- Charolais - Palmer 1972 (67)
- Murray Gray - Richards 1986 (69)
- Hereford - Harper 1986 (71)

Neuraxonal Dystrophy
- Suffolk, Merino, Romney Coopworth, Perendale Sheep — Cordy 1967, Harper 1986, Nuttal 1988 (74-76)
- Cat - Woodard 1974 (81)
- Collie Sheep dog - Clark 1982 (77)
- Rottweiler - Cork 1983 (78)
- Chihuahua - Blakemore 1985 (82)
- Boxer - Griffiths 1980 (87)
- German Shepherd - Duncan 1977 (83)
- Morgan - Beech 1984 (93)

Neurofilamentous Disease
- Yorkshire Pig - Higgins 1973 (97)
- Collie - de Lahunta 1975 (98)
- Cat - Vandevelde 1976 (99)
- Grant Zebra - Higgins 1977 (100)
- Hereford - Rousseaux 1983 (101)

Cerebellum

Dog - Autosomal Recessive
- Kerry Blue Terrier - de Lahunta 1976 (106)
- Gordon Setter - de Lahunta 1980 (114)
- Rough Coated Collie - Hartley 1978 (105)

Dog - Multiple litters
- Airdale
- Bernese Mountain dog
- Finnish Harrier
- Brittany Spaniel
- Border Collie
- Beagle
- Samoyed
- Clumber Spaniel
- Akita

Dog - Single animal or litter
- Miniature Poodle
- Fox Terrier
- Cairn Terrier
- Cocker Spaniel
- Labrador Retriever
- Golden Retriever
- Great Dane
- Schnauzer x Beagle
- Mongrel

Cattle
- Angus
- Holstein
- Ayrshire
- Shorthorn
- Hereford
- Charolais

Sheep
- Merino
- Welsh Mountain
- Corriedale

(Continued)

TABLE I. Concluded

Others
Horse - Arabian, Gotland pony
Yorkshire pig
Cat
Miscellaneous
Peripheral - Schwann cell: Tibetan Mastiff - Cummings 1981 (121)
Spinal Ganglion: English Pointers - Cummings 1981 (123)
Distal Axon: Doberman Pinschers - Chrisman 1985 (125)
Astrocytes
Labrador Retriever - McGrath 1980 (127)
Sheep - Fankhauser 1980 (126)
Scottish Terrier - Cox 1986 (128)

Duchenne's muscular dystrophy in young boys (10,11). In this disease the specific gene locus has been found as well as the structural cell membrane protein — dystrophin — that is deficient in these muscle cells (12). A third example of an inherited myopathy occurs in young Labrador Retrievers. This autosomal recessive inherited disease causes varying degrees of exercise intolerance and was originally described as a Type II muscle fiber deficiency (13,14). A number of clinical variations have been recognized in this breed and are under rigorous study to determine the basic morphological defect and whether they all represent the same genetic abnormality (15-18).

MOTONEURON DISEASE

In this classification the motoneuron is the general somatic efferent lower motor neuron (alpha motoneuron). The cell bodies are in the spinal cord ventral grey column or motor nuclei in the brain stem. The axons are contained in all the spinal nerves and specific cranial nerves (III-VII, IX-XII). This group of motoneuron diseases includes those diseases in which the clinical expression reflects signs of profound neuromuscular disease and the major lesion is in the motoneuron. In some, the disease process is restricted to motoneurons. In others multiple neuronal systems of the central nervous system are affected.

Swedish Lapland Dog

One of the earliest diseases to be described as an abiotrophy was the autosomal recessive neuronal degeneration of young Swedish Lapland dogs by Sandefeldt in 1973 (19). Their neuromuscular weakness began at five to seven weeks of age and rapidly progressed to recumbency with severe muscle atrophy causing joint immobility especially distally. Neuronal degeneration was characterized by chromatolysis, cell body shrinkage, and neuronophagia. This occurred primarily in the ventral grey column of the intumescences of the spinal cord and in the Purkinje neurons of the cerebellar cortex. Other affected neurons included those in spinal cord dorsal grey column, spinal ganglia, trigeminal ganglia and the trigeminal mesencephalic nucleus. This hereditary neuronal abiotrophy was compared to the two common motoneuron diseases in man: Werdnig-Hoffman disease of infants (infantile spinal muscular atrophy) and the Kugelberg-Welander disease which occurs after infancy.

Saint Bernard X Great Dane X Blood Hound

In 1936 Charles Stockard described an inherited disease that became referred to as Stockard's paralysis (20). In his breeding laboratory he was studying skeletal development of large and giant breeds of dog with special interest in the acromegalic condition in Saint Bernards. He raised over 2000 puppies from various cross breedings of Saint Bernards, Great Danes, and Blood Hounds. In a few litters a unique neuronal abiotrophy occurred limited to the motoneurons of the lumbar, intermediate and ventral grey columns. This caused a progressive paraparesis starting at 8 to 14 weeks of age that stopped after a few weeks and some clinical compensation followed. The lesion consisted of an initial chromatolysis followed by neuronophagia and gliosis. An inheritance involving the interaction of three dominant genes was proposed. I am not aware that this disease has ever been seen under natural breeding conditions.

Brittany Spaniel

In 1979 (21,22) Lorenz and Cork provided the first description of an hereditary canine spinal muscle atrophy that occurs in Brittany Spaniels and is inherited as an autosomal dominant gene that has three phenotypic expressions (23). The clinical signs consist of varying degrees of axial and appendicular neuromuscular weakness with atrophy. The homozygous dominant form is expressed as an accelerated neuromuscular weakness with onset around six weeks of age progressing to recumbency by three to four months of age. The heterozygous form is expressed either as an intermediate type with onset of weakness around six months of age and slow progression to three years of age or a chronic type that is not recognized clinically until around one year of age and progresses very slowly with mild signs of neuromuscular weakness. The degree of lesion development correlates with the clinical expression and consists of motoneuronal chromatolysis and proximal axonal swelling with neurofilaments. Motoneurons are affected throughout the spinal cord ventral grey column and in brain stem motor nuclei. Morphometric studies have actually shown an increased population of small neurons in the ventral grey column and axonal atrophy in the ventral roots and spinal nerves. A defect in the normal programmed cell death that occurs during development may be involved in this lesion. The neurofibrillary changes result from an abnormality of the motoneuron cytoskeletal constituents and impaired slow axonal transport (24). The latter has been confirmed in intercostal nerves (25).

Rottweiler

At least three different nervous system abiotrophies have been reported in the Rottweiler breed. One is a spinal muscular atrophy reported by Shell in 1987 (26). Neuromuscular weakness is first observed from birth to four weeks of age and progresses rapidly resulting in recumbency, severe denervation atrophy and joint

immobility. Megaesophagus with regurgitation also occurs. In this study motoneuronal chromatolysis was associated with the accumulation of neurofilaments in the cytoplasm of the cell bodies. These degenerate motoneurons occurred in the spinal cord ventral grey column, especially the intumescences, and in brain stem motor nuclei and the red nucleus (27).

At Cornell we have recently studied a similar disorder in one Rottweiler puppy with onset of weakness at three weeks of age. By eight weeks of age he could only support weight on the forelimbs. Neuromuscular paresis was evident in all four limbs without significant atrophy. At autopsy at ten weeks of age, the swollen chromatolytic motoneuronal cell bodies contained widely dispersed endoplasmic reticulum but few neurofilaments. The affected neurons included those reported by Shell plus neurons in spinal ganglia and many medullary sensory neurons (vestibular, cochlear nuclei) and the cerebellar nuclei. An inherited basis is presumed but not documented.

English Pointers

In 1978 (28) Inada reported an hereditary progressive neurogenic muscular atrophy of English Pointers with onset of progressive neuromuscular signs around five months of age. Usually by three months of progression, these dogs were recumbent and severely atrophied. The affected motoneurons were limited to the spinal cord ventral grey column and spinal accessory nucleus and the hypoglossal nucleus. The degenerative process was unique in that it was accompanied by the accumulation of lipid granules in the cytoplasm of these motoneurons that on ultrastructural study consisted of membranous cytoplasmic bodies and zebra bodies similar to those found in many of the lysosomal storage diseases (29). The presumed enzymatic deficiency is still unknown. Breeding experiments suggest an autosomal recessive inheritance (30).

German Shepherd

A very focal form of motoneuron abiotrophy has recently been studied at Cornell in one of two affected German Shepherd puppies (31). At two weeks of age the female developed a right forelimb weakness; the male was bilaterally weak. This was followed in both by a rapid denervation atrophy with a carpal valgus deformity and fixation of that joint in flexion. A tenotomy was performed in the unilaterally affected female and by five months of age she had good use of this limb with some residual atrophy. The bilaterally affected male was autopsied at eight weeks of age and extensive motoneuron lesions were found only in the ventral grey column of the seventh and eighth cervical spinal cord segments. Many cell bodies were absent and replaced by gliosis. Others were chromatolytic or vacuolated and axonal spheroids were present. The ultrastructural observation of a significant decrease in ribosomes suggests impaired protein synthesis and decreased axonal transport.

MULTISYSTEM — NEURONAL CELL BODY

A multisystem neuronal abiotrophy that primarily affects neuronal cell bodies has been described in Cocker Spaniels, Cairn Terriers and Angora goats.

Cocker Spaniel

In 1988 (32) Zaggy reported on four red-haired Cocker Spaniels with progressive signs of abnormal behavior and ataxia that from the description appears to be predominately a cerebellar ataxia. These signs began at one year of age and progressed for months before autopsy. The lesion consisted of neuronal cell body loss, gliosis and dystrophic axons with widespread distribution in the grey and white matter of most all segments of the brain. No specific topography was evident. Pedigree studies strongly support a familial basis.

Cairn Terrier

In 1988 and 1989 Palmer and Blakemore in England (33,34) and Cummings at Cornell in New York State (35) simultaneously described a similar multisystem neuronal abiotrophy in Cairn Terriers. Correspondence with Farrow in Australia disclosed his experience with the same condition. The report from England concerned three dogs seen in 1974, 1982 and 1985. The disorder appears to be widespread in the breed, of long-standing, and has all the implications of an inherited disorder. A repeat breeding in the United States using related parents produced one affected dog.

The signs are variable but all have onset between 2.5 and 5 months of age and are progressive. In England, the major signs appeared to be a cerebellar ataxia and spinal cord spastic paresis and ataxia. The first dog studied at Cornell was assumed to have cataplexy based on the owner's description of brief episodes of pelvic limb collapse unrelated to exercise and the absence of any abnormality when examined by veterinarians. The second puppy began to first show ataxia and collapsing episodes at ten weeks of age. The signs progressed rapidly and featured two clinical entities. When the puppy was active the signs were those of a severe cerebellar disorder. During this exaggerated activity the dog would suddenly totally collapse and lay completely atonic from which he would recover spontaneously in a few seconds or with stimulation. This latter clinical entity was presumed to be cataplexy.

The lesion in all these Cairn Terriers consists of a widespread chromatolysis of multiple neuronal systems in the central and peripheral nervous systems with widely dispersed endoplasmic reticulum and loss of ribosomes. Peripheral chromatolysis predominates in the spinal cord ventral grey columns. Central chromatolysis is found in brain stem motor and sensory nuclei and a patchy chromatolysis occurs primarily in the spinal cord dorsal grey column, spinal ganglia, enteric and autonomic ganglia. In addition, degenerate processes occur in the spinal cord lateral and ventral funiculi with a unique necrosis of the substantia gelatinosa and adjacent white matter primarily in caudal thoracic and cranial lumbar segments. It is important to differentiate this disease from the inherited globoid cell leukodystrophy that also occurs in this breed.

Angora Goats

In 1987 (36) Lancaster described a possibly inherited neuronal degenera-

tion in young Angora goats. Clinical signs of a progressive spastic paresis and ataxia began from birth to four months and progressed to sternal recumbency and inability to stand in a few weeks. The lesion consists of extensive vacuolation of neuronal cell bodies located diffusely throughout the spinal cord ventral grey column and multiple nuclei of the caudal brain stem and the red nuclei.

MULTISYSTEM — PROCESSES

A number of multisystem degenerations in the nervous system predominate as focal or diffuse lesions involving the axons and myelin of neuronal processes.

Simmental-Limousin

A multifocal encephalopathy was described in the Simmental breed of cattle in Australia and New Zealand in 1989 (37,38). Purebred Simmentals in Australia developed a progressive ataxia and behavioral change at five to eight months of age. The gait abnormality progressed to recumbency with opisthotonos and death by 12 months. In New Zealand both purebred Simmentals and Simmental-Hereford cross cattle at seven months of age developed a progressive paresis and ataxia. This involved primarily the pelvic limbs in the crossbreds and all four limbs in the purebreds. The lesion consists of a unique bilaterally symmetrical severe necrosis of parenchyma with cavitation. Described as a lysis the lesion occurred in the center of each caudate nucleus, internal capsule, and putamen of the cerebrum and various nuclei of the brain stem.

A similar lytic lesion has been observed in Limousin-cross cattle in Great Britain (39) in 1988 and Australia (40) in 1989, but with wider distribution including the optic chiasm, cerebellar peduncles and spinal cord funiculi. The clinical signs begin at four months and consist of a progressive ataxia and visual deficit. No cause has been discovered for this encephalopathy. Ultimately this may turn out to be an environmental toxin and not an inherited abiotrophy.

Brown Swiss

A progressive myeloencephalopathy has been recognized since 1973 (41) in Brown Swiss cattle that are referred to as "weavers" because of their ataxic gait. This progressive paraparesis and ataxia begin around five to eight months of age and predominately affect the pelvic limbs causing a weaving type of gait. Forelimb signs occur later in the course of the disease. Progression occurs over many months (42,43). The major lesion is bilaterally symmetrical degeneration of individual axons and their myelin in the spinal cord white matter especially in the thoracic segments. Similar lesions also occur in the brain stem, cerebellum and subcortical white matter of the cerebrum. A less prominent cell body chromatolysis also occurs in the spinal cord ventral grey column and medullary olivary nuclei (44). Ultrastructural lesions have been described in neuromuscular junctions and skeletal muscles (45). This abiotrophy is thought to be an autosomal recessive inherited condition.

Smooth Fox
and Jack Russell Terriers

A cerebellar ataxia primarily associated with a myelopathy was described in Smooth Fox Terriers in Sweden in 1957 (46) and in Jack Russell Terriers in Great Britain in 1973 (47). The signs begin between 2.5 and 4 months of age and consist of a severe cerebellar ataxia that initially progresses rapidly and then becomes static or progresses slowly. Walking becomes very difficult due to the spasticity, delayed protraction and dysmetria. The gait has been described as bouncing or dancing in quality. Despite the obvious cerebellar nature of the signs, no lesions have been described in the cerebellum. In the Smooth Fox Terriers the only lesion is an extensive bilaterally symmetrical degeneration of the superficial tracts of the lateral funiculi (spinocerebellar) and in the ventral funiculi on either side of the ventral median fissure (48). The Jack Russell Terrier has the same spinal cord lesions but also extensive degeneration in the central components of the auditory system in the brain stem. An autosomal recessive genetic abnormality has been confirmed for the Smooth Fox Terrier and presumed for the Jack Russell Terrier.

Bull Mastiff

In 1983 (49) Carmichael reported on a degenerative brain lesion with hydrocephalus in Bull Mastiffs that was inherited as an autosomal recessive defect. These dogs were six to nine weeks old when their signs began with a visual abnormality and a predominately cerebellar ataxia most evident in the pelvic limbs. Some dogs developed head tremors, abnormal nystagmus and behavioral abnormalities. Hydrocephalus was described as moderate to severe, involving all ventricles and with no recognizable obstruction. Intramyelenic vacuoles created a spongiform change in all the cerebellar nuclei, the vestibular nuclei and caudal colliculi, accompanied by gliosis and spheroids.

German Shepherd

The German Shepherd is a breed predisposed to a degenerative myelopathy in older age. Affected dogs are usually at least four or five years old when they develop an insidiously progressive spastic paraparesis and ataxia of the pelvic limbs. No forelimb deficits are observed. In 1973 (50) Averill described the clinical signs and the associated diffuse degeneration of neuronal processes scattered through all funiculi of the spinal cord. These lesions predominate in the thoracic segments and do not resemble the pattern expected with the process of "dying back of the axons" (51). Lesions also occur in rootlets and spinal nerves but these are also found in clinically normal old animals (52). A family of Siberian Huskies has been reported with this disease (53) and it also occurs sporadically in other breeds (54), especially larger breed dogs (55).

Horses — Appaloosa

In 1977 (56), Mayhew described a degenerative myeloencephalopathy of young horses of many breeds. Onset of a slowly progressive symmetrical spasticity, ataxia, and paresis of all four limbs occurs before seven months in half the cases, between 7 and 14 months in a quarter of the cases and older than that for the rest. The lesion consists primarily of a degeneration of axons and myelin with extensive replacement by astrogliosis. It is a bilaterally symmetrical lesion most

pronounced in the superficial tracts of the lateral funiculi (spinocerebellar) and ventral funiculi adjacent to the ventral surface and ventral median fissure. All spinal cord segments are affected but often the lesion is most advanced in the thoracic segments. Spheroids occur predominately in the nucleus thoracicus and lateral cuneate nuclei. Two causes have been promoted. An environmental insult such as a nutritional deficiency or ingestion of a toxin could account for the multiple cases often seen on the same property. A vitamin E deficiency has been supported by some studies (57) but not others (58). A familial basis has also been advanced and supported in one study involving the Appaloosa breed (59). Further studies are needed to determine this pathogenesis more accurately.

MULTISYSTEM — MYELIN

A few abiotrophies have been described in dogs and cattle that predominately affect central myelin with axonal sparing.

Rottweiler

Gamble in 1984 (60) reported on a leukoencephalomyelopathy in United States' Rottweilers that showed progressive signs of a cervical spinal cord disorder beginning between 1.5 and 3.5 years of age. The predominant lesion was a bilaterally symmetrical primary demyelination with reactive astrocytosis in the central part of the lateral funiculus of the entire spinal cord or predominately the cranial cervical segments. Dorsal funiculi were variably involved and the same lesion occurred in the medullary pyramids and the cerebellar medulla. In addition some spheroids occurred in the general proprioceptive nuclei of the medulla and spinal cord. The same disease has been reported in the Netherlands and a genetic transmission has been proposed (61).

Labrador Retriever

In 1985 (62) O'Brien described a spongy degeneration of the cerebellar white matter in two Labrador Retriever littermates. Their signs began between four and six months of age and initially consisted of episodes of extensor rigidity and opisthotonos (cerebellar seizures?) followed by a progressive cerebellar ataxia. Vacuolated distended myelin sheaths without macrophages were scattered throughout all cerebellar white matter and to a much less degree in spinal nerve myelin (63). The cause remains unknown.

Dalmation

Bjerkas in 1977 (64) described an hereditary cavitating leukodystrophy in Norwegian-bred Dalmations. At three to six months of age, these dogs developed a progressive visual defect and undescribed locomotor abnormality. Their lesions consisted of initially large foci of demyelination with axonal sparing in the centrum semiovale of each cerebrum, the optic nerves, and to a lesser degree the white matter tracts in the basal nuclei (caudate nucleus and putamen) and in the spinal cord white matter. As the lesion progressed, grossly apparent cavities occurred in some of these sites. This disease was presumed to be inherited as an autosomal recessive defect.

Afghan Hounds

In 1978 (65) Cummings described the primary myelinolytic lesion that occurs as an autosomal recessive inherited disorder in young Afghan hounds (66). The signs of white matter spinal cord disease begin between 3 and 13 months in the pelvic limbs with a rapidly progressive spastic paraparesis and ataxia. Paraplegia usually occurs in seven to ten days. Varying degrees of forelimb deficit follow. The lesion consists of a bilaterally symmetrical necrosis of myelin with preservation of axons that appears to start ventrally in the ventral funiculi and expand laterally into the lateral funiculi. Symmetrical dorsal funiculi lesions vary in their occurrence. In all dogs, the processes adjacent to the grey matter (fasciculus proprius) are spared. Only central myelin is affected. Macrophages filled with degenerate myelin accumulate along axons and around blood vessels. A similar myelinolytic lesion occurs around the dorsal nucleus of the trapezoid body in the medulla. Paralyzed dogs can be maintained for months with no further progression of the disease and with persistence of axonal preservation.

Charolais

A unique myelin abnormality in Charolais cattle was first reported from England by Palmer in 1972 (67). These cattle develop a slowly progressive predominately thoracolumbar spastic paraparesis and ataxia sometime between 6 and 36 months of age. The lesion consists of focal areas of demyelination called plaques. These plaques consist of clumps of paranodes where myelin sheaths are distended. These occur in hypertrophied processes of oligodendrocytes at these paranodes (68). Unmyelinated axons traverse these plaques which are located throughout the central nervous system: spinal cord ventral and lateral funiculi, cerebellar medulla and peduncles, transverse fibers of pons, internal capsule in the cerebrum and the corpus callosum. An inherited basis is presumed.

Murray Grey Cattle

In 1986 (69) Richards described a progressive spinal myelopathy in Murray Grey cattle in Australia. These cattle are usually affected at birth with a spastic paraparesis and ataxia. A few calves were normal to 8 to 12 months when signs first began. The signs progress for weeks to months and are associated with a bilaterally symmetrical primary demyelination in the spinal cord lateral and ventral funiculi and a neuronal cell body chromatolysis in the spinal cord, brain stem and cerebellar nuclei. The cause has been determined to be an autosomal recessive inheritance (70).

Polled Hereford

In 1986 (71) Harper described a spongiform encephalopathy of newborn polled Herefords due to a deficiency of a branch-chain ketoacid decarboxylase. A similar disease in children is referred to as maple syrup urine disease. These calves are usually normal at birth but within one to three days rapidly become dull, recumbent and opisthotonic. The lesions consist predominately of a swelling of myelin sheaths around the terminal parts of axons therefore usually adjacent to populations of neurons. This occurs throughout the central nervous system and is probably identical to the hereditary neuraxial edema described

by Cordy in 1969 (72). Whereas the morphological disturbance is expressed mainly in specific areas of central myelin the metabolic abnormality involves neurons diffusely which accounts for the severe widespread nature of the clinical signs (73).

MULTISYSTEM — NEURAXONAL DYSTROPHY

Neuraxonal dystrophy is a neuronal degeneration manifested by axonal swellings called spheroids. These spheroids occur generally in one of three distributions. They may occur in the distal axon at a preterminal site where they usually consist of tubular and/or vesicular membranous organelles. These are usually in or adjacent to populations of neuronal cell bodies (nuclei, cortex). They can occur proximally in the axon near the cell body where the spheroid usually consists of an accumulation of neurofilaments that are often disoriented. A third location of spheroids is at multiple sites along the axon.

Sheep

In 1967 (74) Cordy described a neuraxonal dystrophy in Suffolk sheep that developed a progressive spastic paresis and ataxia primarily related to a spinal cord lesion. The onset of signs varied from 1.5 to 5 months. Spheroids occurred diffusely in the central nervous system at the termination of axons in grey matter areas: all spinal cord grey matter, especially nucleus thoracicus, brain stem medullary nuclei; cerebellar nuclei; rostral colliculi and lateral geniculate nuclei. An autosomal recessive inheritance was proposed for this disease in Suffolk sheep.

In 1986 (75) Harper described a neuraxonal dystrophy in adult Merino sheep in Australia. The signs of progressive diffuse spinal cord disease began between one and four years of age. Spheroids occurred at multiple sites along axons and were found most commonly in areas of white matter: all funiculi of spinal cord, cerebellar peduncles, transverse fibers of the pons, tracts in the thalamus, internal capsule and corona radiata.

In 1988 (76) Nuttall described a central nervous system degeneration in Coopworth sheep in New Zealand that was characterized by spheroid development. These sheep acquired a weaving gait between one and six months that progressed from ataxia and trembling to severe paresis, collapse and death. Spheroids occurred primarily in grey matter areas at the termination of axons: spinal cord dorsal grey columns and nucleus thoracicus, brain stem-lateral cuneate nucleus of medulla, midbrain colliculi, lateral geniculate nucleus of diencephalon, cerebellar nuclei, and optic tracts. An inherited basis was proposed.

Collie Sheep Dog

Clark in 1982 (77) reported on a fairly limited development of spheroids in young working Collie Sheep dogs. The dogs acquired a progressive cerebellar ataxia starting at two to four months of age. Spheroids predominated in terminal axons in the grey matter of cerebellar nuclei and medullary vestibular nuclei. They also occurred in the white matter of cerebellar peduncles and folia. An autosomal recessive inheritance was proposed.

Rottweiler

Cork in 1983 (78) reported a canine form of neuraxonal dystrophy in young adult Rottweilers. The few cases observed developed a slowly progressive cerebellar ataxia starting between one and two years of age (79). There is one report of the same clinical and pathological syndrome in a puppy whose signs began at ten weeks of age (80). In all dogs spheroids predominated in distal axons in numerous grey matter areas: spinal cord dorsal grey columns, especially the nucleus thoracicus; Purkinje neuron layer of cerebellar cortex with significant loss of cell bodies; and medullary general proprioceptive nuclei. An autosomal recessive inherited basis is suspected.

Cat

Woodard in 1974 (8l) described a diffuse neuraxonal dystrophy in young cats that was inherited as an autosomal recessive disease. Affected cats had a coat color similar to the lilac Siamese in contrast to their normal black-coated littermates. Signs of a progressive cerebellar ataxia began around five weeks of age. The spheroids that occurred in regions of grey matter were characterized as ballooned cell processes: olivary nuclei, lateral cuneate nuclei, thalamic nuclei, and mesencephalic reticular formation. Spheroids without ballooning occurred in white matter: medial lemniscus, medial longitudinal fasciculus, central tegmental tract and dorsal rootlets. In addition, neuronal cell body loss and gliosis occurred in cerebellar Purkinje neurons, olivary nuclei, thalamic nuclei and spinal ganglia.

Chihuahua

In 1985 (82) Blakemore described a neuraxonal dystrophy in two Chihuahuas that developed a progressive tremor and ataxia at seven weeks of age. Spheroids occurred in the internal capsule and cerebellar white matter and a variety of nuclei: lateral geniculate, olivary, trapezoid body, and lateral cuneate.

German Shepherd

In 1977 (83) Duncan first reported on a giant axonal neuropathy in German Shepherds that was inherited as an autosomal recessive genetic defect. These dogs developed a progressive pelvic limb paresis and ataxia starting around 15 months of age. Neuromuscular signs predominated (84). Spheroids occurred centrally in the distal part of axons near their termination in grey matter: spinal cord dorsal and intermediate grey columns, medullary general proprioceptive nuclei, and cerebellar granule layer. Others occurred in long white matter tracts near their termination — cranially in dorsal funiculi, caudally in lateral corticospinal pathways, and in the caudal cerebellar peduncles, brachia of rostral colliculi, and vestibulospinal tracts (85). Similar spheroids occurred in peripheral nerves (86). All spheroids consisted of abnormally oriented neurofilaments which may reflect an abnormality in slow axon transport from a primary axonal dysfunction or abnormal cell body metabolic activity.

Boxer

In 1980 (87) Griffiths first reported on a diffuse axonopathy in young Boxers that is inherited as an autosomal recessive disorder. These dogs develop a unique gait abnormality

sometime between one and seven months of age (88). All four limbs are affected but the pelvic limbs are worse. The gait consists of a spastic paresis and severe general proprioceptive deficit causing dysmetria. Reflexes and tone are depressed but no atrophy occurs. After weeks of progression the signs may become static. Spheroids occurred both centrally and peripherally at multiple sites along the axon and consist of accumulated axonal organelles and neurofilaments. Sites include the grey matter of cuneate nuclei, dorsal nuclei of the trapezoid body, and the spinal cord. Affected white matter areas include lateral and ventral funiculi of the spinal cord, optic nerves, and spinal nerve rootlets and proximal nerves (89-91). The rootlet spheroids contain disoriented neurofilaments with a depletion of the cytoskeletal protein tubulin, and increased concentration of actin (92). An inherited primary defect in slow axonal transport is the present understanding of this disease.

Morgan Horse

In 1984 (93) Beech described a very selective focal neuraxonal dystrophy limited to the lateral cuneate (accessory cuneate) nuclei of the medulla of young Morgan horses. Most of these horses first developed a spastic paraparesis and pelvic limb ataxia between 6 and 12 months of age. Occasionally the onset occurs later. No forelimb signs were observed. This morphological lesion does not readily explain a pelvic limb deficit. Breeding studies have supported an inherited basis but the mechanism is not clear. A polygenic defect or a dominant gene with variable expression have been proposed (94).

MULTISYSTEM — CELL BODY NEUROFILAMENTS

A number of degenerative diseases have been described in domestic animals in which the major lesion is a distention of the cytoplasm of neuronal cell bodies with accumulated neurofilaments. Many of these profoundly affect motoneurons and cause signs of neuromuscular disease. This neurofilamentous abnormality has been studied in a variety of human and spontaneously occurring animal disorders and compared to the experimental model produced by iminodiproprionitrile intoxication. This toxin impairs axonal transport resulting in accumulation of neurofilaments proximally in large axons (95,96).

Yorkshire Pig

Higgins described a motoneuron neurofilamentous accumulation in Yorkshire pigs in 1973 (97). These pigs developed signs of progressive neuromuscular disease around five weeks of age. By ten weeks of age the signs were severe. Chromatolysis with intracytoplasmic distention with neurofilaments predominated in the motoneurons of spinal cord ventral grey columns and brain stem cranial nerve motor nuclei. In addition these cell body lesions occurred in the brain stem reticular formation and red nucleus. A myelopathy with spheroids also occurred in the spinal cord lateral and ventral funiculi An inherited basis was presumed.

Collie

In 1974 (98) Shively and I reported a diffusely distributed neuronal cell body neurofilamentous distention including the proximal axons in a young Collie dog. This puppy had signs of a neuromuscular paresis at the time it started to walk and the signs progressed up to euthanasia at 12 weeks. Affected cell bodies included motoneurons of spinal cord ventral grey columns and the oculomotor nuclei; neurons in multiple systems of the medulla, pons, midbrain and diencephalon; cerebellar Purkinje neurons and retinal ganglion cells.

Cat

Vandevelde reported in 1976 (99) on a selective population of motoneurons in a kitten that were distended with neurofilaments. The kitten developed progressive neuromuscular paresis of all four limbs from the time it could walk until it was tetraplegic at ten weeks of age. Affected motoneurons were limited to the lateral part of the ventral grey column of each intumescence.

Grant Zebra

In 1977 (100) Higgins described rapidly progressive signs of neuromuscular paresis in a Grant Zebra foal starting at two weeks of age. By six weeks of age the foal was recumbent, severely atrophied and had immobile joints. Neurofilamentous distention of motoneurons predominated in the spinal cord ventral grey column and brain stem cranial nerve motor nuclei. Other neurons involved were in the reticular formation and red nuclei. Myelopathy also occurred in each lateral and ventral funiculus of the entire spinal cord.

Hereford Cattle

In 1983 (101) Rousseaux described newborn horned Hereford calves as "shakers" because of their diffuse tremors associated with their unsuccessful attempts to stand. A progressive spasticity followed resulting in a few months in complete spastic paraplegia. Neuronal cell body chromatolysis associated with neurofilamentous accumulations in the soma and proximal axon occurred diffusely in numerous brain stem nuclei, cerebellar Purkinje neurons, retinal ganglion cells, all parts of spinal cord grey matter, and sensory and visceral efferent (autonomic) ganglia of the peripheral nervous system. In addition, a degeneration occurred in all funiculi of the spinal cord as well as the ventral rootlets associated with spheroids. An autosomal recessive inheritance was proposed for this disorder (102).

CEREBELLUM

One of the most common of the domestic animal abiotrophies is that which affects the cerebellar cortex (103). Most of these are limited to the Purkinje neurons which appear to be excessively susceptible to intrinsic disturbances of their metabolic apparatus. Because the integrity of the granule cell neuron is dependent on its synaptic relationship with the dendritic zone of the Purkinje neuron, loss of the latter neuron usually results in a secondary depletion of granule cell neurons (104). With a few exceptions retrograde degeneration is not usually observed in other neuronal groups that project to the cerebellar cortex such as the olivary neurons (to Purkinje neurons) and pontine neurons (to granule cell neurons).

The onset of progressive cerebellar ataxia most commonly occurs in the first few weeks [Rough Coated Collie

(105)] or months [Kerry Blue Terrier (106), Holstein calves (107)]. Occasionally it is present at birth [Samoyed (108) and Beagle dogs (109), Welsh Mountain (110) and Corriedale lambs (111), Shorthorn (112) and Hereford calves (113)]. In other instances the onset is delayed and occurs in young adult or older adult animals [Gordon Setter (114), Brittany Spaniel (115), Schnauzer x Beagle dogs (116), Merino sheep (75), and Angus calves (117)]. Occasionally other populations of neurons are involved in the primary abiotrophy [Miniature poodle (118)].

In most instances when enough affected animals have been studied, an inherited autosomal recessive gene has been implicated as the cause. Many reports involve too few animals to confirm a genetic mechanism or involve only a single animal or single litter.

The neuronal abiotrophy of Kerry Blue Terriers that is inherited as an autosomal recessive gene is especially unique because of the additional neuronal populations that are affected besides the Purkinje neurons and the plausible explanation for this unusual topography (106). Signs of progressive cerebellar ataxia begin at 12 to 16 weeks of age and progress usually to an inability to coordinate to stand near a year of age. Autopsies at progressive intervals during the course of the disease reveal an initial Purkinje cell degeneration resulting in profound loss of these cell bodies. As this neuronal population degenerates, the granule cell layer shows a moderate depletion of its cell bodies and after one to two months of progression a bilaterally symmetrical degeneration occurs in the olivary nuclei. These cell bodies become distended with multiple large vacuoles and then disappear. At approximately two to three months of progression of signs, a rapidly progressive degeneration occurs bilaterally in the center of each caudate nucleus. Cell body degeneration is followed by cavitation of these nuclei. This nuclear degeneration is followed in a few weeks by a bilaterally symmetrical degeneration in each substantia nigra (119).

Based on what is known about neurotransmitters and neuroanatomic pathways and the results of injections of kainic acid into neuronal populations in experimental animals, the following hypothesis has been proposed. The primary neuronal degeneration that occurs is an excitotoxic degeneration involving neurons that have glutamate receptors and receive axon terminals that elaborate glutamic acid as the excitatory neurotransmitter (120). Excessive glutamate stimulation will cause degeneration of the neuron stimulated. This could occur if excessive glutamate or an analog is released, astrocytic uptake of glutamate is deficient, or the glutamate receptors are abnormally excessive or bind excessive glutamate. The Purkinje neurons and neurons in the caudate nucleus have glutamate receptors which are activated by the glutamic acid released at synapses from granule cell axons for Purkinje neurons and corticostriate axons for neurons in the caudate nucleus. The olivary and substantia nigra neuronal degenerations are proposed to be secondary retrograde degeneration of cells that terminate on the neurons that have degenerated. The loss of their target cells results in their degeneration. Olivary neurons project directly via climbing fibers on to the dendritic zones of Purkinje neurons. A large population of neurons in the substantia nigra project to neurons in the caudate nucleus — a nigrostriatal pathway. The inherited recessive genetic defect is responsible for the biochemical or structural abnormality involving the neurotransmitter, glutamic acid.

MISCELLANEOUS

A primary inherited Schwann cell defect has been recognized in Tibetan Mastiffs and first reported by Cummings in 1981 (121). At a critical period in the growth of these puppies, when axons are rapidly elongating, these defective Schwann cells cannot keep up with the myelination of these axons and episodes of demyelination and remyelination occur resulting in a hypertrophic neuropathy. The resulting clinical signs of neuromuscular paresis begin between 7 and 12 weeks of age and usually stop progressing after six to seven weeks. Pelvic limb signs and lesions are worse and usually some residual pelvic limb deficit and deformity persists. This Schwann cell defect is inherited as an autosomal recessive disease (122).

In 1981 (123) Cummings described a presumably inherited abnormality of the development and maintenance of somatic afferent nociceptive neurons in English Pointers. This causes these puppies to be analgesic in their paws so that at 11 to 12 weeks of age, they start to lick and chew on their digits causing mutilation with secondary infections and fractures. Spinal ganglia are grossly small from a decreased population of cell bodies and degeneration of cell bodies and processes in the dorsal rootlets. There is a depletion of the nociceptive neurotransmitter, substance P, in the related dorsal grey column of the spinal cord where these nociceptive neurons terminate. In 1964 (124) a similar acral mutilation was described in European short-haired Pointers and called a toe necrosis. An autosomal recessive inheritance was established for this latter disorder.

In 1985 (125) Chrisman described a chronic distal neuropathy in the pelvic limbs of adult Doberman Pinschers. At three years of age or later these dogs develop a peculiar overflexion of the pelvic limbs as they walk. One or both limbs can be affected with what reads like a "stringhalt" type of gait. This is associated with a mild atrophy of caudal leg and thigh muscles. Axonal and myelin degeneration are present distally in neurons of the sciatic nerve.

A unique astrocyte abnormality has been described in humans, sheep and dogs. These affected astrocytes are enlarged and they develop long processes which are distended with intermediate filaments that give them an eosinophilic appearance. These develop primarily in a perivascular and subpial position where the enlarged processes have been called Rosenthal fibers. The perivascular lesions are distributed diffusely throughout the central nervous system but predominately in subpial and subependymal white matter where myelin loss may occur. This has given rise to the term fibrinoid leukoencephalopathy and the eponym Alexander's disease. In 1980 (126) Fankhauser reported this lesion in a four year old Alpine sheep, and McGrath reported it in two six month old Labrador Retrievers (127). In 1986 (128) Cox described the lesion in a Scottish

Terrier that developed a progressive spasticity and ataxia at six months of age and became recumbent by nine months of age.

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